(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: 0 184 470 A2

(12) EUROPEAN PATENT APPLICATION

(21) Application number: 85308916.7

(22) Date of filing: 06.12.85

(51) Int. Cl.[4]: A 61 L 15/06
A 61 L 25/00, A 61 L 15/03

(30) Priority: 07.12.84 US 679653

(43) Date of publication of application: 11.06.86 Bulletin 86/24

(84) Designated Contracting States: DE FR GB

(71) Applicant: MEDTRONIC, INC.
7000 Central Avenue N.E.
Minneapolis Minnesota 55432(US)

(72) Inventor: Jevne, Allan H.
1314 153rd Avenue N.E.
Anoka Minnesota 55303(US)

(72) Inventor: Vegoe, Brett R.
3572 Brookdale Drive
Brooklyn Park Minnesota 55443(US)

(72) Inventor: Holmblad, Carolann M.
R.R. No. 3 Box 277BB
Cambridge Minnesota 55008(US)

(72) Inventor: Cahalan, Patrick T.
10871 133rd Circle
Champlin Minnesota 55316(US)

(74) Representative: Cockbain, Julian Roderick Michaelson et al,
Frank B. Dehn & Co. European Patent Attorneys Imperial House 15-19, Kingsway
London WC2B 6UZ(GB)

(54) Hydrophilic, pressure sensitive biomedical adhesive composition.

(57) A hydrophilic, skin-compatible, pressure sensitive, adhesive gel/hydrogel composition comprising: 25 to 50 weight pecent polyvinyl pyrrolidone (PVP) having a weight average molecular weight of at least about 100000, and preferably in the range of about 100,000 to 600,000; 2 to 5 weight percent polyvinyl alcohol (PVA) preferably having a weight average molecular weight in the range of about 150,000 to 300,000; 5 to 41 weight percent polar plasticizer or humectant; 3 to 50 weight percent water; and about 0 to about 50 weight percent of a further ionic or non-ionic species. In a preferred aspect, the composition of the invention is suitable for use in an iontophoresis device to provide a hydrophilic gel matrix from which a drug is iontophoretically delivered.

HT 149-476

Hydrophilic, Pressure Sensitive Biomedical Adhesive Composition

This invention relates to a novel, hydrophilic, skin-compatible, pressure sensitive, adhesive composition. the composition of the present invention is referred to as a "gel" or "hydrogel" and is particularly advantageous in biomedical applications such as sensing or stimulating electrodes, in electrosurgery (e.g. an electrocautery ground electrode), wound management or drug delivery. In a preferred practice of the invention, the present adhesive gel is useful in active or passive transdermal drug delivery. In yet another preferred practice of the present invention, an ionic species including ionic drugs or salts may be included in the present composition giving an increase in its conductivity.

U.S. Patents 4292302, 4292303, 4289749 and 4294820 describe a polymeric diffusion matrix in which there is dispersed terbutaline, clonidine, phenylpropanolamine and phenylephrine, respectively. These four patents in the name of Alec D. Keith et al. and commonly assigned to Key Pharmaceuticals Inc., differ only in having different drugs, the incorporation of which is described below in each patent. As will be more completely described below, the polymeric drug diffusion matrix of the Keith et al. patents suffers the drawback of being unstable with respect to the water and humectant included therein. Put otherwise, the drug diffusion matrix of the Keith et al. patents tends to synerese, i.e. to exude the liquid, water component of the gel.

United States Patent No. 4460562 also to Keith et al. titled "Polymeric Diffusion Matrix Containing

Propranolol" describes a diffusion matrix comprising from about 1 to about 60% of a polar plasticizer (e.g., glycerol), from about 6 to about 30% by weight of at least 90% hydrolyzed polyvinyl alcohol having a molecular weight of about 50,000 to about 150,000, from about 2 to about 30% by weight polyvinyl pyrrolidone having a molecular weight of about 15,000 to about 85,000 and a pharmaceutically transdermally effective amount of propranolol. As is more completely discussed hereinafter in the Examples, this material has poor adhesion to skin, does not have good elongation and also tends to synerese. Furthermore, the materials of the Keith et al. patents are not pressure sensitive adhesives.

It is an object of the present invention to provide gel compositions having superior properties to the prior art compositions as represented for example by the polymeric diffusion matrices of Keith et al.

We have found that by selection of the composition components and their relative concentrations within certain ranges, hydrophilic, pressure sensitive biomedical adhesive compositions having particularly good fluid retention (e.g. non-exudation of the water component) can be produced.

According to the present invention we thus provide a skin-compatible hydrophilic adhesive composition comprising about 25 to 50 weight per cent, preferably about 30 to 40 weight percent, polyvinyl pyrrolidone (PVP) having weight average molecular weight of at least about 100000; about 2 to 5 weight percent (preferably about 3 to 4 weight percent) polyvinyl alcohol (PVA); about 5 to 41 weight percent polar plasticizer or humectant; about 3 to 50 weight percent water; and from about 0 to 50 weight percent of a further ionic or non-ionic species.

For the compositions of the invention the nature of the further ionic or non-ionic species

will depend on the intended use of the composition. Thus the further species for example may be a pharmaceutically effective amount of a desired drug or may be sufficient or an ionic species to provide conductivity to the composition. Generally speaking, the amount of an ionic species or a drug (which may also be ionic) would be from about 0 to 50 weight percent, conveniently 0 to 22 weight percent of the composition.

As noted above, the compositions according to the present invention have been found to exhibit the critically important property of not syneresing (i.e. exuding water or humectant). The compositions of the first four of the Keith et al. patents mentioned above is generally in the range of 2 to 10 weight percent polyvinyl pyrrolidone, 6 to 20 weight percent polyvinyl alcohol, 2 to 60 weight percent polar plasticizer (e.g. glycerol or polyethylene glycol) and a pharmaceutically effective amount of a drug. While no particular range of water is disclosed or claimed in any of the Keith et al. patents, the examples in, e.g., U.S. Patent No. 4294820 indicate weight percentages of water of 45, 70, and 66. Thus, consistent with the above description of the present invention, the critical advantage acheived herein by virtue of having a higher molecular weight PVP and different amounts of PVA and PVP is a stable, non-syneresing, adhesive composition. For a preferred iontophoretic use of the present composition the low concentration of ionic impurities provides more efficient iontophoretic drug delivery. The critical advantages achieved by the present composition are more fully described in the Examples which follow.

The present invention contemplates the utilization of generally from 25 to 50 weight percent polyvinyl pyrrolidone (PVP) with a preferred range of 30 to 40 weight percent. The polyvinyl pyrrolidone employed

in the present invention conveniently has a weight average molecular weight in the range of about 100,000 to 600,000, preferably falling in the range of about 300,000 to 400,000. A particularly suitable polyvinyl pyrrolidone as employed in the present invention is type NP-K90 commercially available from the GAF Corp. Chemical Products.

The present invention also contemplates the presence of polyvinyl alcohol in a weight percentage of about 2 to 5, preferably about 3 to 4, weight percent. A particularly advantageous polyvinyl alcohol such as can be employed in the present invention is sold by E.I. Du Pont de Nemours & Co. under the trade designation "Elvanol HV". Generally speaking, polyvinyl alcohol suitably employed in the present invention would conveniently have a weight average molecular weight in the range of 150,000 to 300,000, preferably about 170,000 to 220,000. A particularly preferred PVA is the material available from E.I. Du Pont de de Nemours & Co. having a stated molecular weight of about 185,000.

The polyvinyl alcohols of this invention conveniently are generally at least about 75% hydrolyzed. Preferably, useful PVA is about 100% hydrolyzed. Percentage of hydrolysis is not thought to be critical in this invention.

The present invention also contemplates the presence of from about 5 to 41 percent, preferably about 15 to 25 weight percent, polar plasticizer or humectant, e.g. glycerol. Other useful polar plasticizers include propylene glycol, sorbitol, poly(ethylene) glycol (preferably having a molecular weight in the range of about 200 to 20,000) and polypropylene glycol (preferably having a molecular weight in the range of about 500 to 5,000). Other polar plasticizers or humectants will be well-known to one skilled in the hydrogel art.

The present invention also contemplates the presence of about 3 to 50 weight percent water in the resulting matrix. Deionized water is preferred. This percentage of water, which is advantageously maintained in the present composition, provides suitable adhesiveness, tack, cohesive strength, and skin-compatibility.

Furthermore, the present invention optionally contemplates the presence of a further ionic or non-ionic species, e.g. a drug (which may be ionic or non-ionic). The selection of the further species, e.g. a particular salt or drug, will be dependent upon the intended utilization of the completed composition. If the present adhesive composition is to be used to hold an iontophoresis electrode in contact with a patient's skin and to provide a reservoir for the drug, then the drug which is to be iontophoretically delivered would be mixed in the present matrix. If the present composition is to be employed to maintain an electrocardiogram electrode in place and to provide a quality sensing capability, then a suitable ionic species, e.g. KCl, would be employed in the composition to provide the desired conductivity. While both drug or a conductive salt are optionally included in the present composition, the present composition may be employed in other applications, (e.g. wound dressings) which do not require a conductive material, in which case neither a drug nor an ionic species would be present.

One skilled in the present art will recognize that it is possible to add small amounts of other materials to adjust the properties of the present composition for a particular end use. Such further additives may conveniently constitute from about 0 to about 22 weight percent of the compositions of the invention. For example, if it is desirable to increase the tackiness of the gel, poly-2-acrylamido

2-methyl propane sulfonic acid (poly(AMPS)) (or its salts) may be employed. Other materials which can be employed to increase tackiness include polyacrylic acid, polystyrene sulfonic acid or salts thereof, karaya, xanthan, quar or lucust bean gums. Tackifiers above described would if used generally be present in the range of about 2 to 22 weight percent.

For some applications, it may be desirable to increase the internal coherence, cohesiveness or strength of the biomedical compositions. In such instances, materials such as hydroxy propyl methyl cellulose, carboxy methyl cellulose, hydroxy propyl quar, dextran or silica may be added. One skilled in the present art will recognize other materials which could be added to the composition described herein to adjust the various desired properties. Generally speaking, such additives would be present in the range of about 0 to 10 weight percent.

Preparation of the compositions of the present invention is relatively straightforward. Generally speaking, a temperature-controlled, stirrable reactor is employed. Thus a reactor might be preheated to about 90°C, set to mix at approximately 100 revolutions per minute, and the following materials (in representative quantities):

1.	deionized H_2O	39 weight percent
2.	glycerol polar plasticizers (Mallinckrodt, Inc.)	22 weight percent
3.	polyvinyl alcohol (Du Pont Elvanol HV)	4 weight percent
4.	polyvinyl pyrrolidone (GAF Company 360,000 molecular weight)	35 weight percent

would be mixed, preferably in the order indicated.

The temperature of the closed mixer then would be increased to approximately 130°C while maintaining stirring. After a temperature of approximately 130°C is obtained, the temperature of the mixture would be decreased to approximately 95°C, the mixer subsequently turned off and the material poured onto a release paper (e.g. "Polyslick"), the gel thereby being cooled to a solid, non-liquid state.

The compositions of the invention will now be further illustrated by the following non-limiting Examples:

EXAMPLES 1-8

Using the general procedures set out above, 8 gels were prepared. These materials were then evaluated for their adhesion to skin, adhesion to 304 stainless steel, ultimate tensile strength, 100% secant modulus and percent elongation. The tendency to synerese of these materials also was subjectively evaluated. The compositions of the respective Examples and the evaluations are set out in Table I:

TABLE I

Composition ** (% w/w)	Example Number 1	2	3	4
360,000 MW PVP	32	31	36	29
Elvanol HV PVA	4	4	3.5	4
40,000 MW PVP	-	-	-	-
115,000 MW PVA	-	-	-	-
Glycerol	24	22	-	24
Sorbitol	-	-	5	-
PEG 600	-	-	15	-
D.I. H_2O	35	35	34	27
KCl	5	-	-	-
Na Acetate	-	8	6.5	-
Na Salicylate	-	-	-	16
% skin adhesion	20	20	35	70
***Adhesion to 304 S.S.	136(52)	45(17)	91(35)	45 (17)
++Ultimate tensile st.	10(69)	15(103)	35(241)	15(103)
++100% Secant modulus	3(21)	8(55)	10(69)	4 (28)
% Elongation	700	700	800	900
Syneresis*	No	No	No	No

** MW = average molecular weight
D.I. = deionized
PEG = polyethylene glycol
* to the point of exuding liquid
‡ comparison Examples
*** in g/in, figures in brackets in N/m
++ in p.s.i., figures in brackets in kPa

TABLE I (continued)

Composition ** (% w/w)	Example Number 5	6‡	7‡	8‡
360,000 MW PVP	40	-	-	-
Elvanol HV PVA	4	-	-	4
40,000 MW PVP	-	30	8	32
115,000 MW PVA	-	6	15	-
Glycerol	-	20	30	24
Sorbitol	-	-	-	-
PEG 600	16	-	-	-
D. I. H_2O	40	39	47	35
KCl	-	5	-	5
Na Acetate	-	-	-	-
Na Salicylate	-	-	-	-
% skin adhesion	60	0	0	0
***Adhesion to 304 S. S.	136 (52)	<5 (2)	0 (0)	<5 (2)
++Ultimate tensile st.	17 (117)	14 (97)	125 (862)	4 (28)
++100% Secant modulus	5 (34)	5 (34)	51 (352)	1 (7)
% Elongation	650	240	190	170
Syneresis*	No	Yes	Yes	Yes

Several observations may be made about the data contained in Table I. First of all, the test procedures employed for the various measurements taken were as follows:

<u>Skin adhesion:</u> The percentage indicated is the approximate area of a patch of test material remaining in intimate human skin contact after a 6 hour wearing period. A zero reading means that the test patch of material did not adhere to skin through the entire 6 hour period of the test.

<u>Adhesion to 304 stainless steel:</u> The numbers indicated are the force needed to peel a 1"x5" (25mm x 127mm) strip of the test material from the indicated substrate. Samples were smoothed onto the stainless steel substrate by hand and all air bubbles squeezed out. The samples then were permitted to rest for 24 hours before the test was run. The numbers are averages of the force needed to peel the sample from the substrate using an Instron tensile tester at a cross head speed of 5 inches per minute (127mm/min).

<u>Ultimate tensile test:</u> Using an "Instron" tensile tester, the tensile strength of the various samples was determined using a cross speed of 5 inches per minute (127mm/min), 10 pounds force (44N) full scale load. 1"x2" (25mm x 51mm) rectangular samples were employed, ultimate tensile strength being the maximum force applied (to breaking) divided by the cross-sectional area of the sample.

<u>100% secant modulus:</u> 100% secant modulus was determined by dividing the force applied when the sample had been stretched 1 inch (25mm) (in the above tensile test) by the cross-sectional area of the sample.

<u>Percent elongation at break:</u> This is calculated by dividing the distance the cross-head (e.g. of an "Instron" tensile tester) had travelled to sample

break by the original length of the sample and multiplying the result by 100.

The first 5 examples in Table I are materials of the present invention. The material of Example 6 is one prepared substantially in accordance with Keith et al. US Patent No. 4460562. Example 7 was prepared in accordance with Keith et al. US Patent No. 4393302. Example 8 is prepared substantially the same as the material of Example 1 (i.e. a material of this invention) with the exception that the preferred lower molecular weight PVP of the Keith et al. patent was employed. An examination of the results indicates that all three of the materials of comparative Examples 6-8 tended to synerese. Further, the three materials did not provide identifiable adhesion to skin and exhibited poor adhesion to stainless steel. Percent elongation at break was also very low. Tensile strength and secant modulus were greater for the comparative materials than for the materials of the present invention. This was due to the fact that the material of this invention is comfortable and elastomeric. These data illustrate the importance of the molecular weight and composition percentage differences of the material of this invention versus that of prior art as represented by the Keith et al. patents.

EXAMPLES 9-12

Using the general synthetic process described above, a number of gels of the present invention were prepared utilizing different additives to enhance tackiness of the resulting gel. The compositions of these materials are set out in Table II. In each of Examples 9-12, the polyvinyl pyrrolidone was the 360,000 molecular weight material commercially

available from GAF. The polyvinyl alcohol was "Elvanol HV" available from E.I. Du Pont de Nemours & Co. In Examples 9 and 10, the additive was poly(2-acrylamido 2-methyl propane sulfonic acid) commercially available from Henkel Corporation under the trade designation "Rheothik 80-L". In Example 11, the additive was karaya and in Example 12 polyacrylic acid "Goodright K732" commercially available from Goodyear Chemicals. These Examples illustrate how in accordance with another aspect of the invention where the compositions contain a tackifier then the PVP content may be reduced to as low as about 13 weight percent provided the PVP and the tackifier together constitute at least about 23 weight percent of the composition. Thus, generally the tackifier additive may replace a portion of the PVP.

TABLE II

Example No.	PVP Wt.%	PVA Wt.%	Glycerol Wt.%	Water Wt.%	Tack Enhancer %W/W
9	28.9	3.5	36.2	26.7	4.7
10	16.8	4.9	37.8	34.3	6.2
11	18.0	4.0	41.0	22.0	15.0
12	13.8	5.0	37.2	22.0	22.0

EXAMPLES 13-15

A number of compositions of the invention were prepared in accordance with the above procedures in which additives were included to increase the cohesive strength of the gel. In Example 13, 3.0 weight percent hydroxy propyl guar was employed. In Example 14, 5.1 weight percent of silica ("M-5 Cabosil") commercially available from Cabot Corporation was employed. In Example 15, 3% weight hydroxypropyl methyl cellulose was employed. Overall compositions of the respective materials of Examples 13-15 are shown in Table III.

TABLE III

Example No.	PVP Wt.%	PVA Wt.%	Glycerol Wt.%	Water Wt.%	Strength Enhancers %W/W
13	31	4.0	22.0	40	HPG 3% Hydroxy-propyl guar
14	29	4.0	25.0	37	M-5 silica 5%
15	31	4.0	22.0	40	HPMC 3%

EXAMPLES 16-19

A number of different compositions contemplated by the present invention were synthesized using the procedure above in which various polar plasticizers were substituted for the plasticizer glycerol. In Example 16, sorbitol, commercially available from Aldrich Chemical, was employed. In Examples 17 and 18, poly(ethylene glycol) molecular weight 600 was employed. In Example 19, poly(propylene glycol) molecular weight 725 was employed. The overall compositions of the materials of Examples 16-19 are set forth in Table IV.

TABLE IV

Example No.	PVP Wt.%	PVA Wt.%	Water Wt.%	Polar Plasticizer %W/W
16	33.0	4.0	28.0	41.0
17	40.0	4.0	40.0	41.0
18	28.6	4.0	35.0	37.1
19	33.0	4.0	30.0	41.0

EXAMPLE 20

An electrocardiogram (ECG) electrode gel according to the invention was prepared utilizing polyvinyl pyrrolidone, PVA, glycerol, deionized water and potassium chloride. The material was tested on an ECG electrode and showed acceptable electrical characteristics with respect to impedance, offset voltage, instability, defibrillation offset, defibrillation recovery and 10Hz alternating current impedance.

EXAMPLE 21

A composition of the present invention was synthesized according to the above procedure and employed as a stilumating gel with a transcutaneous electronic nerve stimulator unit. Acceptable electrical stimulation was found particularly when silica ("Cab-0-Sil M-5") was employed in the 4-6 wt. percent range.

EXAMPLE 22

A composition of the present invention was employed in conjunction with pilocarpine nitrate (Sigma Chemical Corporation) to demonstrate the effectiveness of the present composition as an iontophoresis gel. Pilocarpine nitrate was iontophoretically driven into a subject's skin thus inducing delivery of sweat and demonstrating the utility of the present compositon as an iontophoresis electrode adhesive/drug reservoir material.

EXAMPLE 23 (Comparative)

To a beaker at ambient temperature 30g glycerol and 45ml water were added and mixed. The beaker and mixture was heated. When 70°C was reached,

15g of 100% hydrolyzed 115,000 molecular weight polyvinyl alcohol and 8g 40,000 molecular weight polyvinyl pyrrolidone were added. Heating and stirring were continued until the mixture reached the temperature of 90°C and all ingredients were in solution. The mixture then was poured onto a release paper to a thickness of 2 to 3mm and was permitted to cool until gelation occurred.

The synerese characteristics of this comparative material prepared above (0.125 in. (3 mm) thick) then were monitored. Approximately 59.8g of the gelled material was placed between two sheets of Polyslick release liner and sealed into a polyethylene bag. Over time, the weight of the gelled material in the bag was as follows:

24 hr: 54.5g*
28 hrs: 51.5g*
72 hrs: 48.9g*
96 hrs: 46.6g*
1 week: 44.5g*
2 weeks: 40.8g*
* liquid in the bag

Utilizing the test procedures described above, the ultimate tensile strengh was measured to be 125 psi (862 kPa), the 100% modulus was 51 psi (352 kPa) and the percent elongation was determined to be 190%. From these data and observations, it is seen the prior art material (e.g. of the Keith et al. patents) does not exhibit the stability and desirable performance characteristics of the material of this invention.

Claims

1. A skin-compatible, hydrophilic adhesive composition comprising:

25 to 50 weight percent polyvinyl pyrrolidone having a weight average molecular weight of at least about 100000;

2 to 5 weight percent polyvinyl alcohol;

5 to 41 weight percent polar plasticizer or humectant;

3 to 50 weight percent water; and

about 0 to 50 weight percent of a further ionic or nonionic species.

2. A composition as claimed in claim 1 wherein there is from about 30 to 40 weight percent polyvinyl pyrrolidone.

3. A composition as claimed in either of claims 1 and 2 wherein there is about 3 to 4 weight percent polyvinyl alcohol.

4. A composition as claimed in any one of claims 1 to 3 wherein the polyvinyl pyrrolidone has a weight average molecular weight in the range of about 100,000 to 600,000.

5. A composition as claimed in any one of claims 1 to 4 wherein the polyvinyl pyrrolidone has a weight average molecular weight in the range of about 300,000 to 400,000.

6. A composition as claimed in any one of claims 1 to 5 wherein the polyvinyl alcohol has a weight average molecular weight in the range of about 150,000 to 300,000.

7. A composition as claimed in any one of claims 1 to 6 wherein the polyvinyl alcohol has a weight average molecular weight in the range of about 170,000 to 220,000.

8. A composition as claimed in any one of claims 1 to 7 wherein the polar plasticizer comprises a material selected from glycerol, sorbitol, and poly(ethylene) glycol.

9. A composition as claimed in any one of claims 1 to 8 further containing from about 0 to about 22 weight percent of an additive.

10. A composition as claimed in claim 9 where said additive is selected from the group consisting of hydroxy propyl methyl cellulose, carboxy methyl cellulose, cellulose, hydroxy propyl quar, dextran, silica, poly(AMPS) and salts thereof, polyacrylic acid and salts thereof, polystyrene sulfonic acid and salts thereof, karaya gum, xanthan gum, quar gum and locust bean gum.